Received: 25 March 2022 | Revised: 30 September 2022 | Accepted: 3 October 2022

DOI: 10.1002/psp4.12878

ARTICLE

Comparative analysis of PD-1 target engagement of dostarlimab and pembrolizumab in advanced solid tumors using ex vivo IL-2 stimulation data

Daren Austin[1] | **Murad Melhem**[2] | **Yash Gandhi**[3] | **Sharon Lu**[2,4,*] | **Sandra Visser**[3]

[1]GSK, Brentford, UK

[2]GSK, Waltham, Massachusetts, USA

[3]GSK, Collegeville, Pennsylvania, USA

[4]Eyepoint Pharmaceuticals, Watertown, Massachusetts, USA

Correspondence
Daren Austin, GSK, 980 Great West Road, Brentford, Middlesex, TW8 9GS, UK.
Email: daren.j.austin@gsk.com

Funding information
GlaxoSmithKline

Abstract

Dostarlimab (JEMPERLI) is an anti-programmed cell death protein-1 (PD-1) monoclonal antibody (mAb) which is approved by the US Food and Drug Administration for patients with recurrent/advanced mismatch repair-deficient solid tumors, including endometrial cancer, following progression on prior treatment, with approval based on data from the phase I GARNET trial. To support dostarlimab dose regimen recommendations, we estimated and compared the potency of dostarlimab relative to anti–PD-1 mAb pembrolizumab using both data published from the KEYNOTE-001 trial of pembrolizumab and data from the GARNET trial. PD-1 target engagement was assessed ex vivo in blood samples via a super antigen staphylococcal enterotoxin B stimulation assay and interleukin-2 (IL-2) stimulation ratios calculated for dostarlimab. A non-linear mixed-effect sigmoid maximum effect inhibitory model was fitted to dostarlimab IL-2 stimulation ratios using extracted pembrolizumab data as informative priors. The estimated half-maximal effective concentration was 1.95 μg ml^{-1} (95% credibility interval: 0.21–5.87) for dostarlimab and 1.59 μg ml^{-1} (95% confidence interval: 0.42–6.12) for pembrolizumab. These findings suggest dostarlimab and pembrolizumab to be equipotent for peripheral PD-1 suppression based on analysis of ex vivo IL-2 stimulation ratios. Accounting for a three-fold dilution between serum and tumor, a target dostarlimab trough concentration of ~54 μg ml^{-1} would be needed for 90% suppression in the tumor. These data support the use of dostarlimab as a potent PD-1 suppressor and the recommended dostarlimab monotherapy dose regimen of 500 mg Q3W ×4 cycles followed by 1000 mg Q6W thereafter in recurrent/advanced solid tumors.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Anti–PD-1 monoclonal antibody dostarlimab demonstrated durable clinical activity and acceptable safety in recurrent/advanced solid tumors in the phase I

*Affiliation at the time of study analyses.

[Correction added on 23 November 2022, after first online publication: The copyright line and legal statement was changed.]

GARNET trial and is approved for recurrent/advanced mismatch repair deficient/microsatellite instability-high advanced solid tumors following progression on prior treatment.

WHAT QUESTION DID THIS STUDY ADDRESS?

Characterization of dostarlimab pharmacology, including the potency of PD-1 blockade as compared to pembrolizumab, to support monotherapy dosing regimen recommendations for recurrent/advanced solid tumors.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

IL-2 stimulation ratios indicate dostarlimab has an half-maximal effective concentration of 1.95 $\mu g\,ml^{-1}$ and is deemed equipotent to PD-1 inhibitor pembrolizumab based on published data. The approved dostarlimab dosing regimen of 500 mg Q3W ×4 cycles and 1000 mg Q6W thereafter is likely to maintain maximal PD-1 suppression throughout dosing cycles.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?

These modeling analyses demonstrate the utility of published data for comparing the pharmacology of novel treatment agents with similar targets.

INTRODUCTION

Monoclonal antibodies (mAbs) targeting immune checkpoint proteins, such as programmed cell death protein-1 (PD-1) and programmed death ligands 1 and 2 (PD-L1 and PD-L2), have successfully been used to help reinstate immune surveillance and improve anticancer immunity in numerous cancer indications.[1,2] Dostarlimab (JEMPERLI) is a humanized anti–PD-1 immunoglobulin G4 (IgG4) mAb that binds the PD-1 receptor with high affinity, blocking its interaction with PD-L1 and PD-L2.[3] Based on data from the phase I GARNET study (NCT02715284), dostarlimab monotherapy was approved by the US Food and Drug Administration (FDA) for the treatment of recurrent/advanced mismatch repair deficient (dMMR) recurrent/advanced solid tumors, including endometrial cancer, following progression on prior treatment, and is also approved by the European Medicines Agency (EMA) for dMMR/ microsatellite instability-high (MSI-H) endometrial cancer following progression on or after platinum-based chemotherapy. Population pharmacokinetic (PK) analyses of GARNET data demonstrated that dostarlimab's PK parameters and time-dependent linear elimination are in line with other anti–PD-1 mAbs.[4] Patient and disease characteristics were found to exert limited to moderate impact on exposure, and clinically significant efficacy and safety exposure–response relationships were not identified. Dostarlimab exhibits dose-proportional PKs with no weight-based effect, supporting flat dosing.

The recommended therapeutic dose regimen for dostarlimab is 500 mg every 3 weeks (Q3W) for four cycles followed by 1000 mg once every 6 weeks (Q6W).[5,6] This study aimed to estimate and compare the potencies of the anti–PD-1 mAbs pembrolizumab and dostarlimab to support the justification of the recommended dose regimen for recurrent/advanced solid tumors in addition to GARNET efficacy, safety,[7–10] population PKs, and exposure–response analyses. To assess PD-1 blockade potency, an established interleukin-2 (IL-2) stimulation assay was utilized, which can be used as a measure of PD-1 target engagement due to IL-2 production being enhanced by PD-1 blockade.[11] A modeling analysis was then conducted using the ex vivo whole blood IL-2 stimulation data and serum concentrations from a previous study of pembrolizumab in advanced solid tumors (KEYNOTE-001).[11,12] Individual patient-level data from the KEYNOTE-001 study were extracted, digitized, and then applied in this modified analysis to dostarlimab ex vivo IL-2 stimulation data from the GARNET study, in order to compare the relative potency of pembrolizumab with dostarlimab, a similar anti–PD-1 mAb. Here, we present the full results of these modeling analyses.[13]

METHODS

Data sources and sampling

Individual dostarlimab IL-2 stimulation ratio data was available from parts 1 (dose escalation) and 2A (fixed-dose safety evaluation phase) of the GARNET study, for which the study design has previously been reported.[9] Blood samples for IL-2 stimulation ratio analyses and dostarlimab serum measurements were collected at baseline (cycle [C] 1 and day [D] 1 predose), C1D3, C1D5, C1D15, C1D22, C1D29 (1000 mg only), C2D1, and C5D22 at doses of 1, 3, and 10 $mg\,kg^{-1}$ every 2 weeks (Q2W), 500 mg Q3W, and 1000 mg Q6W.

Pembrolizumab individual patient-level serum concentrations and IL-2 stimulation ratios across doses of 0.005–10 mg kg^{-1} were extracted digitally from published KEYNOTE-001 study data.[11] As per published methods, these data were derived from blood samples collected at baseline, C1D1, C1D7, C2 predose (day 14), and C6 predose. Serum concentrations were determined concurrently in part A of the study (dose escalation) and part A1 (expansion cohorts) or predicted using a population PK model for part A2 (additional cohort implemented to better estimate pembrolizumab PK/pharmacodynamic [PD] properties).

Datasets from the KEYNOTE-001 and GARNET studies were collated in spreadsheets, post-processed for coding of visits, log-transformed, and combined into two SAS analyses datasets. The data were analyzed using Bayesian methods with the same sigmoid maximum effect (E_{max}) model as pembrolizumab (methods described further below).

IL-2 simulation assay

In both the GARNET and KEYNOTE-001 studies, whole blood samples were stimulated with Staphylococcal enterotoxin B, either with or without the addition of 25 μg ml^{-1} pembrolizumab or dostarlimab for 4 days at 37.8°C.[11] IL-2 concentration was measured in both aliquots with a lower limit of quantitation, 4 pg ml^{-1}. The stimulation ratio was calculated as the IL-2 concentration in the aliquot with spiked anti–PD-1 mAb over that in the aliquot treated with staphylococcal enterotoxin with a spiked IgG4 control.

PK/PD modeling analyses

For dostarlimab and pembrolizumab data, IL-2 stimulation ratios were normalized to the predose value and log-transformed.

A nonlinear sigmoid, E_{max} model was first fitted to log-transformed pembrolizumab IL-2 stimulation ratio data. The model was parameterized in terms of baseline (E0), E_{max}, log_{10}-transformed half-maximal effective concentration (EC_{50}; LOG10EC50), and Hill coefficient (SLP). A random intercept (b1) was included in the model for individual data (part A1 only) with a fixed variance (between-patient baseline variance [s2b1] = 0.3; Supplementary Methods, Code 1). Due to missing patient identifier information in part A2, s2b1 was fixed to zero (i.e., no random effects) and data were reweighted without random effect to account for this.

Dostarlimab data were fitted first to a mixed-effects model repeated measurement (MMRM) model, and least-squares mean treatment differences from baseline were estimated, using the SAS code presented in Supplementary Methods, Code 2. The data were subsequently described using the same E_{max} model used for pembrolizumab, including weakly informative priors from the initial pembrolizumab modeling analyses (Supplementary Methods, Code 3). The weakly informative priors based on parameters estimated from pembrolizumab included E0, E_{max}, LOG10EC50, SLP (all simple normal distributions), residual variance (EPS), and s2b1 (inverse-gamma distributions). Acceptable convergence was confirmed using Effective Sample Size (ESS) and Geweke diagnostics, following which model inference was conducted using Markov Chain Monte Carlo (MCMC) sampling of 100,000 posterior samples with 10% thinning to remove autocorrelations (where present) for all parameters of interest, then summarized graphically.[14] SAS 9.4 software was used for all analyses. Model selection was based on parameter precision, parsimony, and Bayes Information Criteria. Model goodness of fit was also evaluated graphically.

RESULTS

Pembrolizumab IL-2 ratio analyses

Pembrolizumab IL-2 stimulation ratio E_{max} model parameters are presented in Table 1. The EC_{50} for inhibition of IL-2 stimulation for pembrolizumab was 1.59 μg ml^{-1} (95% confidence interval [CI] 0.42–6.12), and the EC_{50}, E_0, E_{max}, and SLP were all estimated with acceptable precision. Final model predictions of pembrolizumab exposure response showed close correspondence for observed and predicted data (Figure 1).

Dostarlimab IL-2 ratio analyses

Based on an IL-2 stimulation ratio of 0.5 indicating a maximal IL-2 response, all dostarlimab doses showed, as anticipated, a reduction in IL-2 adjusted mean ratio compared to baseline ex vivo conditions, with 95% CIs of 0.25–1.0 (Figures 2 and 3). A dose of 1 mg kg^{-1} did not reach an adjusted mean ratio to baseline of 0.5 at any visit and showed statistical separation from the ratios for a dose of 10 mg kg^{-1} at the end of the first cycle (Figure 3), providing statistically significant evidence of dose/exposure response.

Dostarlimab Bayesian exposure–response IL-2 ratio analyses

The nonlinear mixed-effects E_{max} model with informative priors was found, after satisfactory model convergence, to

TABLE 1 Pembrolizumab E_{max} model parameter estimates

Parameter	Estimate	Standard error	DF	*p* value	Alpha	Lower CI limit	Upper CI limit
E0[a]	1.01	0.08	116.00	<0.0001	0.05	0.85	1.17
E_{max}[a]	−0.30	0.19	116.00	0.12	0.05	−0.68	0.08
$LOG10EC_{50}$	0.20	0.29	116.00	0.49	0.05	−0.38	0.79
SLP	0.52	0.18	116.00	<0.01	0.05	0.16	0.88
EPS	0.10	0.01	116.00	<0.0001	0.05	0.07	0.12

Abbreviations: CI, confidence interval; DF, degrees of freedom; E_0, baseline IL-2 stimulation ratio; EC_{50}, concentration resulting in half maximal response; E_{max}, maximal effect; EPS, residual variance; IL-2, interleukin-2; $LOG10EC_{50}$, log_{10}-transformed EC_{50}; SLP, Hill coefficient.

[a]Zero on the log-scale is equal to one untransformed.

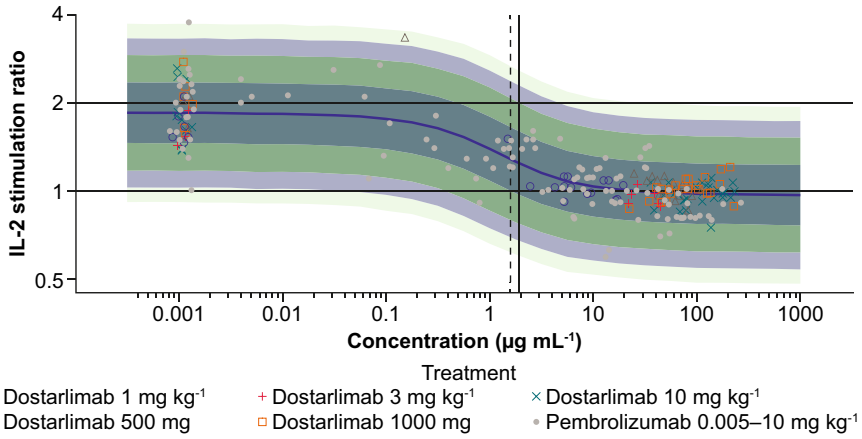

FIGURE 1 IL-2 stimulation exposure–response analyses for pembrolizumab and dostarlimab. Solid dark blue line represents dostarlimab median IL-2 stimulation ratio, light blue band shows the interquartile range, green shows the interdecile range, light blue shows the 90% CI, and light green shows the 95% CI. Dostarlimab (solid) and previous pembrolizumab (dashed). Dostarlimab EC_{50} indicated by solid vertical line and pembrolizumab EC_{50} indicated by dashed vertical line. CI, confidence interval; EC_{50}, concentration of half maximal response; IL-2, interleukin-2.

describe the data well and deemed suitable for inference by sampling of the posterior distribution using MCMC sampling. The final model equation was:

$$\text{LOG2RATIO} = \text{b1} + \text{E0} + \frac{(\text{EMAX} - \text{E0})\text{DVSLP}}{\text{DVDLP} + (10 * * \text{LOG10ED50})\text{SLP}} + \text{RESID}$$

$$\text{fRO} = 2 * * \text{LOG2RATIO}$$

Between-patient variability

$$\text{BSV} = \text{SQRT}(\exp(\text{S2B1}) - 1) = 39\,\%$$

Residual error

$$\text{BOV} = \text{SQRT}(\exp(\text{EPS}) - 1) = 35\,\%$$

Code for fitting the model to the data is shown in the Supplementary Methods. The final model-estimated dostarlimab EC_{50} for inhibition of IL-2 stimulation was 1.95 μg ml^{-1} (Highest Probability Density [95%] credibility interval: 0.21–5.87). The final model-estimated dostarlimab E0 for inhibition of IL-2 stimulation was 0.9 μg ml^{-1} (Highest Probability Density [95%] credibility interval: 0.72–1.08), E_{max} −0.05 (−0.26–0.14), LOG10EC50 0.10 (−0.69–0.75), SLP 1.41 (0.21–2.57), EPS 0.11 (0.08–0.15), and S2B1 0.14 (0.08–0.21; Table 2). Individual model predictions showed a close fit for observed and predicted IL-2 ratios (Figure 2). The final dostarlimab IL-2 stimulation ratio data, with individual dostarlimab and pembrolizumab data overlaid, are shown in Figure 1. Pembrolizumab and dostarlimab appear to be equipotent, supported by the similar predicted EC_{50s} of 1.95 and 1.59 μg ml^{-1}, respectively.

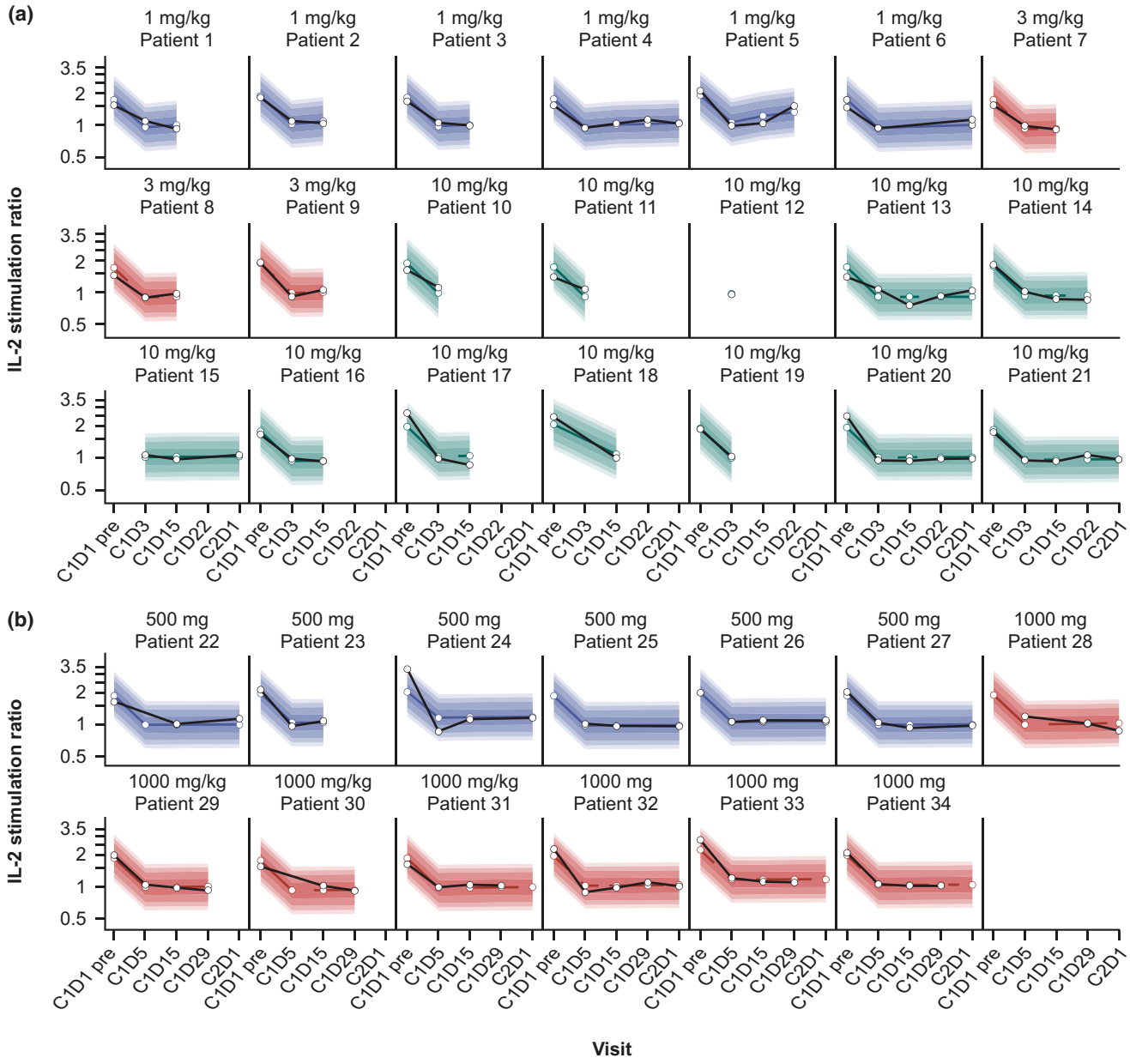

FIGURE 2 Overlays with goodness of fit modeling of the observed and individual-predicted IL-2 ratios following dostarlimab administration for (a) weight-based doses and (b) fixed doses. Model predictions are shown by colored data lines, observational measurements shown by black data lines. The shaded regions show the 95% prediction interval for the individual observation. Only one data point was available for patient 12. C, cycle; D, day; IL-2, interleukin 2; pre, predose.

DISCUSSION

In this study, we utilized published data from the KEYNOTE-001 study of pembrolizumab in ex vivo modeling analyses to assess the pharmacology of dostarlimab with regard to its potency of PD-1 inhibition and to estimate dostarlimab doses required to suppress peripheral PD-1 activity.[11,12] The EC_{50} for the KEYNOTE-001 dataset, including data for doses of 0.005 to 10 mg kg^{-1}, was 1.59 μg ml^{-1}, well estimated, and in agreement with previously published values.[11] Based on the model-estimated EC_{50} of 1.95 μg ml^{-1} for dostarlimab, pembrolizumab and dostarlimab appear to be equipotent at suppressing peripheral PD-1 stimulation. However, the informative prior $\log10EC_{50}$ of −0.5 suggests that pembrolizumab has a fivefold higher efficacy in vitro.

All dostarlimab doses showed reduced IL-2 stimulation ratios compared to baseline at all post-treatment assessments. However, based on the IL-2 stimulation ratio not reaching 0.5 at any visit, a dostarlimab dose of 1 mg kg^{-1} is considered insufficient to maintain modulation of peripheral PD-1 activity across the dosing cycle,

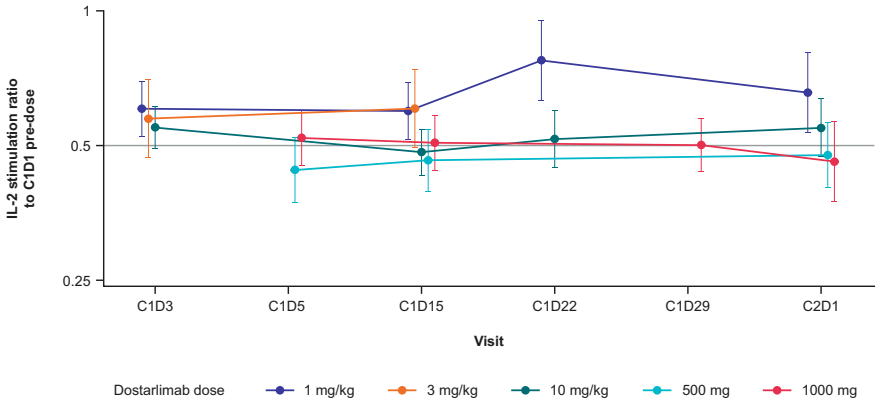

FIGURE 3 Dostarlimab adjusted mean IL-2 stimulation ratio compared to baseline. Data represent the adjusted mean ± 95% CI. C, cycle; CI, confidence interval; D, day; IL-2, interleukin 2.

TABLE 2 Final E_{max} model PK/PD parameter estimates for dostarlimab

PK/PD parameter (unit)	*N*	Mean	Standard deviation	Median	HPD credibility limit lower	HPD credibility limit upper
E0[a]	10,000	0.90	0.09	0.90	0.72	1.08
E_{max}	10,000	−0.05	0.12	−0.04	−0.26	0.14
LOG10EC_{50}	10,000	0.10	0.38	0.12	−0.69	0.75
EC_{50} (μg ml^{-1})	10,000	1.95	4.31	1.30	0.21	5.87
SLP	10,000	1.41	0.62	1.34	0.21	2.57
EPS	10,000	0.11	0.02	0.11	0.08	0.15
S2B1 (E0)	10,000	0.14	0.04	0.14	0.08	0.21

Abbreviations: E0, baseline IL-2 stimulation ratio; EC_{50}, concentration resulting in half maximal response; E_{max}, maximum effect; EPS, residual variance; HPD, highest probability density; IL-2, interleukin-2; LOG10EC_{50}, log_{10}-transformed concentration resulting in 50% of maximum effect; PK/PD, pharmacokinetic/pharmacodynamic; SLP, Hill slope; S2B1, between-patient baseline variance.

[a]The random effect is the intercept, which is added to E0 (effect at 0).

thereby implying that the clinical dose should be higher than 1 mg kg^{-1}, particularly to maintain target engagement in the tissue. To help further establish the recommended dostarlimab dose regimen, estimation of the dose required for PD-1 suppression at the tumor site is pertinent. Below the dose required for complete antigen saturation, the uptake of antibody entering a tumor site scales linearly with the dose concentration,[15] allowing inferences to be made for dose scaling required to reach antigen saturation, and thereby activity at the tumor. Based on the EC_{50} of 1.95 μg ml^{-1}, a target dostarlimab trough concentration of 18 μg ml^{-1} is needed to maintain 90% of maximal peripheral PD-1 suppression, and a concentration of ~54 μg ml^{-1} would be needed for 90% suppression in the tumor, assuming a typical threefold dilution factor for penetration into tumor tissues.[16] Based on an established population PK model,[4] simulations showed that the median model-predicted minimum concentration values were 39.3 mg L^{-1} for the first dose (500 mg Q3W) and 67.9 mg L^{-1} at steady state (1000 mg Q6W) and more than 98% of simulated patients achieved minimum serum concentrations higher than 18 mg L^{-1} for the recommended dose regimen (500 mg Q3W ×4 cycles followed by 1000 mg Q6W). Additionally, mean serum trough levels of dostarlimab exceed concentrations required to ensure maximal receptor occupancy after the first dose of the regimen.[17] Collectively, these data suggest that both regimens are likely to be sufficient in maintaining PD-1 suppression in patients with solid tumors.

Whereas data are based on an ex vivo assay, and intratumor PD-1 modulation may differ from that measured in the blood,[11] dostarlimab was shown to be equipotent to pembrolizumab, and the clinical efficacy of pembrolizumab is well-established in a variety of advanced solid tumors across a dosing range of 2–10 mg kg^{-1}.[5,18,19] This suggests that, provided both antibodies exert similar physiological effects and tissue disposition is also similar,[16] dostarlimab should prove as effective at suppressing PD-1 activity at the tumor site as pembrolizumab, and thereby as efficacious. Although the doses evaluated in the GARNET study (1, 3, and 10 mg kg^{-1} and 500 mg and 1000 mg fixed doses) may be considered too high to fully characterize the pharmacology of dostarlimab, the observation that the lowest dostarlimab dose evaluated of 1 mg kg^{-1} appears insufficient for maintaining peripheral PD-1 suppression throughout the dosing interval provides confidence that

the recommended dosing range is appropriate without the need for clinical evaluation of a wider dosing range, and notably subtherapeutic doses.

In this study, weakly informative priors were based on parameters estimated for pembrolizumab in the KEYNOTE-001 study.[11] Pembrolizumab parameters were used for these analyses given both the similarities in the mechanism of action of pembrolizumab and dostarlimab and the availability of the data from the KEYNOTE-001 study. Additionally, the absence of sufficiently low exposures in part A of the KEYNOTE-001 study (i.e., 1 mg kg^{-1} being the lowest starting dose), meant that EC50 and slope were poorly estimated.[11] Weakly informative priors from the pembrolizumab analysis were therefore used for satisfactory model convergence and good description of the data.

This study has several strengths and limitations. A key study strength is that these modeling analyses demonstrate the utility of published datasets for comparing the pharmacology of novel treatment agents. Additionally, this study supported selection of the approved dose regimen of dostarlimab for recurrent/advanced solid tumors.[5,6] However, this study also has several limitations. We were not able to apply the full model used to fit IL-2 stimulation data from KEYNOTE-001 analyses directly due to the absence of sufficiently low dostarlimab exposures. However, the use of published parameters as weakly informative priors and successful model convergence resulted in a model that described the data well and was deemed suitable. Variability in the data was observed, which may be due to the small sample sizes with available IL-2 stimulation data from the GARNET study, suggesting supplementation with a larger data set would allow more robust analysis. We do not believe that there is any influence of weakly informative priors on the point estimate in our model. This is because previous literature has indicated that impact of priors is highly dependent on model complexity.[20] The model used here is not complex and data around the EC_{50} estimate does exist in our model and the pembrolizumab model, where priors came from. Additionally, examples of models where weak or diffuse priors have been shown to adversely impact final model estimates include probit regression models, meta-analysis, item response theory, latent growth mixture models, and multilevel structural equation models.[20] In all these cases, researchers found that diffuse priors had a substantial negative impact on the obtained estimates, but this is not the case for our model. Additionally, we believe that the simulations shown in Figures 1–3 illustrate that the data are well described. A Monte Carlo simulation could further strengthen the findings of our modeling analyses and should be considered in future studies. Finally, data from part A2 of the KEYNOTE-001 study were not identifiable at the patient-level due to missing patient-identifier information. As such, a random intercept could not be included in the modeling analysis and between-patient baseline variance was fixed to zero for the modified E_{max} model. However, the final point estimate of EC_{50} for dostarlimab is not expected to have been affected as data were insensitive to the removal of the random effect (data not shown).

In summary, the results presented indicate that dostarlimab and pembrolizumab are equipotent PD-1 inhibitors, as assessed by ex vivo IL-2 stimulation ratios. Doses of dostarlimab 500 mg Q3W or 1000 mg Q6W both maintain maximal peripheral PD-1 suppression levels throughout the dosing interval, supporting that both regimens could be used alone or in sequence. While considering the increased patient convenience of a Q6W dosing regimen compared with Q3W, a patient-centric regimen of dostarlimab 500 mg Q3W for four doses followed by 1000 mg 6QW was evaluated in an expansion cohort phase of the GARNET study. This study, in combination with GARNET efficacy, safety,[7–10] population PKs, and exposure–response analyses,[4] supports this approved dose regimen for dostarlimab monotherapy of 500 mg Q3W for four doses followed by 1000 mg Q6W in recurrent/advanced solid tumors.[5]

AUTHOR CONTRIBUTIONS

All authors wrote the manuscript. D.A. designed the research. D.A., M.M., Y.G., S.L., and S.V. performed the research. D.A. analyzed the data.

ACKNOWLEDGMENTS

Editorial support (in the form of writing assistance, including development of the initial draft, assembling tables and figures, collating authors comments, grammatical editing, and referencing) was provided by Elisabeth Walsby, PhD, and Victoria Hunter, MSc, at Fishawack Indicia Ltd., UK, part of Fishawack Health.

FUNDING INFORMATION

The GARNET study (NCT02715284; 215333) and this analysis were funded by GSK. Trademarks are owned by or licensed to the GSK group of companies. Medical writing support was funded by GSK.

CONFLICT OF INTEREST

D.A. is an employee of GSK and holds stock/ownership interests and has patents planned, issued, or pending. M.M., Y.G., and S.V. are employees of GSK and hold stock/ownership interests. S.L. was an employee of GSK who held stock/ownership interests at the time of the study. Trademarks are owned by or licensed to the GSK group of companies.

DATA AVAILABILITY STATEMENT

Anonymized individual patient data and study documents can be requested for further research from www.clinicalstudydatarequest.com.

ORCID

Daren Austin https://orcid.org/0000-0002-9346-5071

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Austin D, Melhem M, Gandhi Y, Lu S, Visser S. Comparative analysis of PD-1 target engagement of dostarlimab and pembrolizumab in advanced solid tumors using ex vivo IL-2 stimulation data. *CPT Pharmacometrics Syst Pharmacol*. 2023;12:87-94. doi:10.1002/psp4.12878